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Review

Do angiotensin converting enzyme inhibitors improve walking distance in patients with symptomatic lower limb arterial disease? A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background: Several studies have reported the clinical effects of long-term treatment with cardioprotective medications in patients with lower limb peripheral arterial disease (PAD) in terms of reducing cardiovascular morbidity and mortality. A number of these studies investigated the clinical effect of angiotensin converting enzyme inhibitors (ACEIs) on walking distance in this group of patients.
Objective: To review the evidence regarding the effects of ACEIs in patients with symptomatic PAD of the lower limbs in terms of the effect on maximum and pain-free walking distances and ankle brachial pressure index (ABPI).
Methods: A systematic literature search of the medical literature from 1966 to 2010 on randomized placebo-controlled trials which assessed the effect of ACEIs on maximum and/or pain-free walking distances and/or ABPI in patients with symptomatic lower limbs PAD was performed. Data from included studies were pooled with use of random-effects model with standard mean differences. Heterogeneity across studies was assessed with calculation of I^2 statistic.
Results: From a total of 346 publications identified, 34 articles were selected for full review based on title and abstract. 4 RCTs comprising 576 patients (334(58%) males, mean age 60.7 years, age range (58–66)) met the inclusion criteria and were systematically reviewed. Of those, 137 (24%) patients suffered from symptomatic lower limb PAD. Maximum walking distances were pooled successfully from all 4 studies. After analysing these data, we found significant heterogeneity among the groups and no significant difference in the pooled treatment effect (standard mean difference = 0.46, 95% CI (−0.99–1.92), $p = 0.53$, I^2; = 95%). Pain-free walking distances and ankle brachial pressure indices were pooled successfully from 3 studies and showed an insignificant overall treatment effect (standard mean difference = 0.97, 95% CI (−0.24–2.18), $p = 0.12$ and 0.68, 95% CI (−0.70–2.06), $p = 0.33$, respectively).
Conclusion: The evidence regarding ACE inhibition efficacy on treadmill walking distance in patients with intermittent claudication is contradicting and lacked properly powered RCTs. However, based on this study, ACEIs did not improve treadmill walking distance and ABPI in patients with symptomatic lower limb arterial disease. Further research from properly powered RCTs is needed.

1. Introduction

Lower limb peripheral arterial disease (PAD) is a common disorder. An Ankle Brachial Pressure Index (ABPI) which is diagnostic of PAD is found in approximately 12% of adults above the age of 50 years.[1] Of those, almost a third experience pain on walking or intermittent claudication.[2] PAD is an important marker of cardiovascular risk and is associated with mortality 3–5 times that of an aged matched population mainly due to cardiac and cerebrovascular events. The overall prognosis for the patient with PAD is poor with a cumulative annual mortality of up to 5%. In claudicants, however, the prognosis for the limb is more benign with 75% of patients' symptoms remaining stable/improving with only a small minority progressing to critical ischaemia. It has been recommended that patients with PAD should have aggressive secondary prevention and management of risk factors.[3–7]

Over the last decade, intensive research has investigated the potential clinical benefits of angiotensin converting enzyme inhibitors (ACEIs). The renin angiotensin system (RAS) plays a major role in cardiovascular disease. ACEIs competitively inhibit the angiotensin

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Table 1
Summary of studies included in the systematic review.

Ref. No	First author	Year	Type	Jadad score	Total No. of patients	Type of ACEI	Dose	Follow up	Outcome
16	Roberts et al	1987	RCT	4/5	23	Captopril	50 mg/day	6 months (1 month treatment)	No effect on pain free and maximum walking distances
17	Spence et al	1993	RCT	4/5	23	Cilazapril	2.5 mg/day	8 weeks	No effect on leg blood flow & adverse effect on walking time on a treadmill
18	Overlack et al	1994	RCT	4/5	490 (54 with clinical PAD)	Perindopril	4 mg/day	6 weeks	No effect on pain free and maximum walking distances
2	Ahimastos et al	2006	RCT	5/5	40	Ramipril	10 mg/day	24 weeks	Improved pain free and maximum walking distances

converting enzyme which is a non specific enzyme involved in the metabolism of many small peptides. This includes the conversion of angiotensin I, an inactive octapeptide, into angiotensin II. Inhibition of the angiotensin converting enzyme will reduce the levels of angiotensin II and increase the levels of bradykinin; the latter stimulates the synthesis of nitric oxide (NO) which plays a vital role in vasodilatation and inhibition of vascular hypertrophy.[8] ACEIs also promote an elastogenic profile in the extracellular matrix of the arterial wall by increasing elastin and decreasing the levels of matrix metalloproteinases.[9] These effects of ACEIs improve vascular endothelial function in PAD patients.

Long term ACE inhibition in PAD patients with no evidence of left ventricular dysfunction or heart failure is supported by level-1 evidence of clinical efficacy in reducing cardiovascular morbidity and mortality and health economic analyses of cost effectiveness.[10–14] However, perhaps due to the relatively high incidence of side effects and concerns regarding deterioration in renal function in patients with silent renal artery stenosis, ACE inhibition has not been universally accepted into the arsenal of secondary prevention measures in PAD patients. It is conceivable that increased ACEIs prescribing in this patient group may occur if there was clear evidence of associated improvement in disease specific symptoms.

This study aims to review the evidence supporting ACEIs use in patients with symptomatic PAD in terms of effect on maximum walking distance as a primary outcome measure and pain-free walking distance and/or ABPI as secondary outcome measures.

2. Methods

2.1. Search strategy

A systematic search of literature was performed in the medical databases: MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). In addition, we searched conference proceedings and the reference lists of relevant articles to identify articles missed by the electronic searches. The keywords 'angiotensin converting enzyme inhibitors,' OR 'angiotensin converting enzyme inhibitors,' OR 'ACE inhibitors,' AND 'peripheral arterial disease,' OR 'peripheral arterial occlusive disease,' OR 'intermittent claudication,' were used along with their synonyms. Limits: English language, involving humans and randomised controlled trials were applied.

2.2. Inclusion criteria

Studies were eligible to be included in our review if they were: 1. Randomised controlled trials which compared any kind of ACEIs with placebo or no treatment 2. Included patients with symptomatic peripheral arterial disease of the lower limbs (intermittent claudication) as either the study population or a subgroup 3. Used maximum and/or pain-free walking distances and/or ABPI as outcome measures 4. Minimum period of treatment with ACEIs is one month and 5. Published in English from 1966 until present. A summary of these studies can be found in Table 1. We excluded studies which compared ACEIs combined with any other drug with placebo.

2.3. Quality and data extraction

Quality was assessed using the Jadad five-point scale for randomised trials.[15] The following data were recorded for each study: First author, year of publication, patients' characteristics (total number of patients, number of patients with symptomatic PAD, age, and sex), ACEI type and dose, duration of treatment, follow up period and outcome. Two independent reviewers (YS and FM) extracted and checked the studies included. Disagreements between the reviewers were resolved by consensus.

Authors of one of the selected studies[2] have been contacted successfully to obtain unpublished data in order to complete a meta-analysis. In studies where mean maximum and/or pain-free walking times were reported,[2,17] they were converted to distances using the treadmill speeds reported in those studies.

2.4. Statistical analysis

For both treatment groups in the included studies[2,16–18] standard mean differences and 95% confidence intervals were calculated based on means and standard deviations extracted from individual studies. One study[16] reported mean and standard error. We converted standard error to standard deviation by using a standard formula.[19] Treatment effect was significant if $p < 0.05$. Heterogeneity between studies was tested with use of both the chi square test (significant if $p < 0.1$) and the I^2 test (with substantial heterogeneity defined as values $> 50\%$). As studies showed significant heterogeneity, a random-effects model was used to calculate the pooled effect sizes.

Review Manager (version 5.0, The Cochrane Collaboration 2008) was used for data analysis.[20]

3. Results

3.1. Literature search

The search identified 346 potentially eligible studies of which 312 studies were excluded on title and abstract. Full articles of the

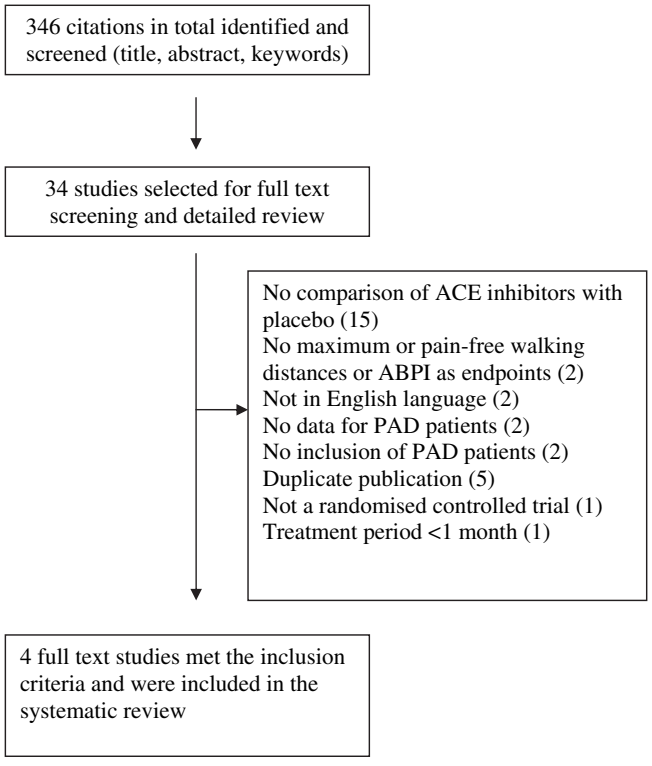

Fig. 1. Study flow diagram of systematic review and exclusion criteria.

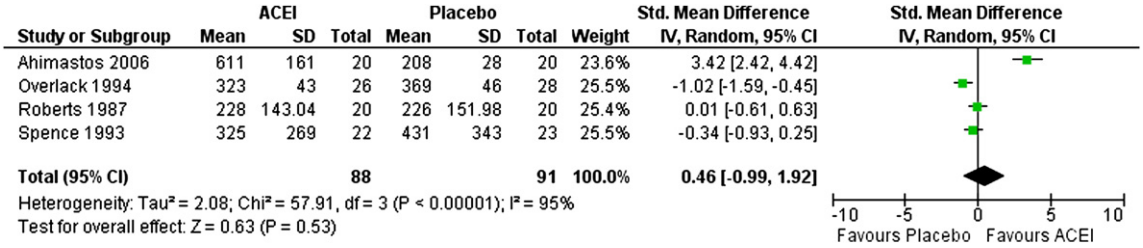

Fig. 2. Forest plot illustrating pooled maximum treadmill walking distance. CI: confidence interval, SD: standard deviation, IV: inverse variance.

remaining 34 studies were collected and evaluated. 4 studies met our inclusion criteria and were included in the systematic review. Study flow diagram and exclusion criteria are presented in Fig. (1).

3.2. Patient's characteristics

Studies included a total of 576 patients. There were 334 (58%) males and 242 (42%) females, with a mean age of 60.7 years, age range (58–66). 137 (24%) patients had symptomatic peripheral arterial disease of the lower limbs (intermittent claudication).

3.3. Description of included studies

A double blind, placebo- controlled, crossover trial of antihypertensive treatment in 23 patients with hypertension and peripheral arterial disease, failed to demonstrate any statistically significant benefit of captopril 25 mg twice daily over placebo in terms of pain free and maximum walking distances (149 ± 71.5 m vs. 145 ± 89.4 m and 228 ± 143 m vs. 226 ± 151.9 m, respectively).[16] Captopril preserved lower limb arterial circulation possibly by maintaining the collateral blood supply which could be attributed to the lack of angiotensin II vasoconstriction effect caused by ACE inhibition and reduced breakdown of bradykinin.

Indeed, a placebo controlled, crossover, RCT of ACE inhibition with cilazapril (2.5 mg/day) for 8 weeks in 23 claudicants demonstrated a deleterious effect on treadmill walking time.[17]Mean maximum treadmill walking time was longer in the placebo group 8.04 ± 6.39 min (431 ± 343 m) than the cilazapril group 6.05 ± 5.01 min (325 ± 269 m), $p < 0.009$. ABPI was higher, but statistically insignificant, after treatment in the placebo group than the cilazapril group (0.69 ± 0.12 vs. 0.66 ± 0.15), $p > 0.05$.

A multicentre, double blind, RCT of 54 patients with essential hypertension and claudication (Fontaine IIb) randomised to perindopril 4 mg o.d ($n = 26$) or matching placebo ($n = 28$) for 6 weeks found that there was a slight but not a statistically significant increase in pain-free walking distance in favour of the perindopril group (173 ± 17 m vs. 165 ± 10 m).[18] In terms of maximum walking distance, patients in the placebo group walked a significantly longer distance than the perindopril group (369 ± 46 m vs. 323 ± 43 m, respectively). This difference was found to be statistically insignificant according to the authors. There was no difference in the ABPI in both groups after treatment (0.75 ± 0.05).

Finally, a further double blind trial randomised 40 intermittent claudicants with superficial femoral artery disease to either ramipril 10 mg once daily or matched placebo for 24 weeks (20 patients per group) and found ramipril in comparison to placebo to be associated with statistically significant improvements in pain- free walking time, 381 ± 124 s (339 ± 110 m) in the ramipril group vs. 161 ± 29 s (143 ± 26 m) in the placebo group, $p < 0.001$. This was also the case for maximum treadmill walking time, 687 ± 181 s (611 ± 161 m) in the ramipril group vs. 234 ± 31.4 s (208 ± 28 m) in the placebo group, $p < 0.001$, ankle brachial pressure indices at rest and post exercise and Walking Impairment Questionnaire scores[2] The changes in ABPI with ramipril (0.73 ± 0.09 in the ramipril group vs. 0.50 ± 0.10 in the placebo group, $p < 0.001$) were found to be due to a reduction in brachial systolic blood pressure at rest and both a reduction in brachial systolic blood pressure and an increase in ankle pressure post exercise.

Ahimastos et al.[2] used strict inclusion criteria which limited the applicability of the results to non diabetic patients with infrainguinal arterial disease.

3.4. Outcome measures reporting

All four studies evaluated maximum walking distance/time.[2,16–18] Three studies evaluated pain free walking distance/time[2,16,18] and ABPI.[2,17,18]

3.5. ACEIs effect on maximum treadmill walking distance

Maximum walking distances/times were pooled successfully from four studies.[2,16–18] After analysing these data, we found significant heterogeneity among the groups and no significant difference in the pooled treatment effect (standard mean difference = 0.46, 95% CI (−0.99–1.92), $p = 0.53$, $I^2 = 95\%$) (Fig. 2).

3.6. ACEIs effect on pain-free treadmill walking distance

Pain free walking distance/time could be pooled from three studies.[2,16,18] Analysis of these data showed significant heterogeneity

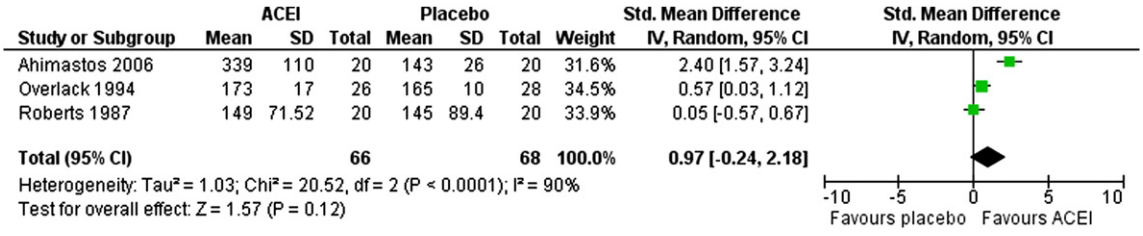

Fig. 3. Forest plot illustrating pooled pain-free treadmill walking distance. CI: confidence interval, SD: standard deviation, IV: inverse variance.

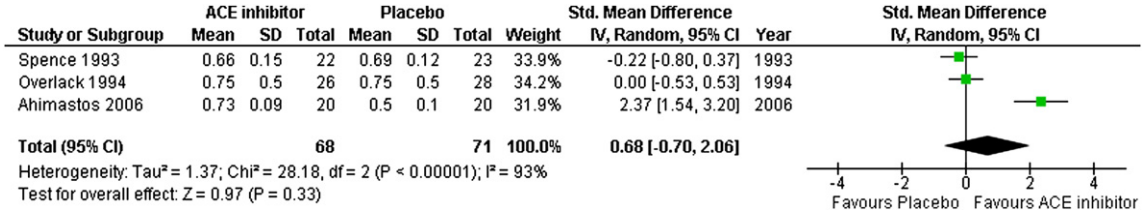

Fig. 4. Forest plot illustrating pooled Ankle Brachial Pressure Index. CI: confidence interval, SD: standard deviation, IV: inverse variance.

and no significant differences in the pooled treatment effect (standard mean difference = 0.97, 95% CI (−0.24–2.18), $p = 0.12$, $I^2 = 90\%$) (Fig. 3).

3.7. ACEIs effect on ABPI

Ankle Brachial Pressure Indices were also pooled from three studies[2,17,18] and analysis of data showed significant heterogeneity and no significant differences in the pooled treatment effect (standard mean difference = 0.68, 95% CI (−0.70–2.06), $p = 0.33$, I^2p2; = 93%) (Fig. 4).

3.8. Side effects and withdrawals due to treatment with ACEIs

In Overlack et al,[18] out of 253 patients randomised to receive perindopril, 4(1.5%) patients suffered from cough. 8 (3.2%) patients in the perindopril group withdrew, of those, 1 patient withdrew due to cough. Other studies did not report any side effects and/or withdrawals due to treatment with ACEIs.

4. Discussion

This review has highlighted the contradicting evidence regarding the impact of ACE inhibition on treadmill walking distances in patients with PAD; as 3 out of 4 studies reported negative results; however, these studies were not properly powered and two of them were crossover trials.[16,17] Crossover trials are not likely to be suitable for evaluating disease progression and severity because treatment effects are not fully reversible after each treatment. Moreover, the variation in findings may reflect variability in patient subgroups, disease distribution, and dose/duration of treatment. Long term (>24 weeks) treatment of non diabetic patients with isolated infrainguinal disease would seem to infer maximal benefit.

Further data from properly powered randomised controlled trials is required to analyse the effectiveness of ACEIs for symptom relief, generic and disease specific quality of life and perhaps the vascular endothelium in patients with intermittent claudication.

4.1. Study strengths and limitations

The strengths of this meta-analysis include a comprehensive literature search which included only randomised controlled trials, duplicate data extraction and duplicate assessment of quality of evidence using the Jadad 5-point scale for randomised trials.[15] Moreover, authors of unpublished data were contacted to clarify areas of concern and to provide unreported data which consisted of unreported means and standard deviations in one study.[2] We successfully managed to obtain unreported data from the author, which made it possible to do a meta-analysis.

However, this meta-analysis had some limitations, including the high heterogeneity among the included studies and the small number of studies which have been found in the literature. Therefore, results from this meta-analysis should be interpreted with caution.

Conflict of interest/funding

The authors declare that there are no conflict of interests and no sources of funding for this work.

Ethical approval

None declared.

Author contributions

YS searched the literature, reviewed the articles, extracted and analyzed data and prepared the manuscript.

FM searched the literature, reviewed the articles and extracted data.

IC reviewed the included studies and revised the final manuscript.

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